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(54) Title: TREATMENT OF TYPE 2 DIABETES WITH INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

(57) Abstract: A method of treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease, which comprises the administration to the individual of repeated doses of an inhibitor of dipeptidyl peptidase IV or a prodrug thereof.

TREATMENT OF TYPE 2 DIABETES WITH INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

FIELD OF THE INVENTION

The present invention relates to a method for delaying the onset of type 2 diabetes and alleviating the physiological consequences of type 2 diabetes.

BACKGROUND

Diabetes mellitus affects about 5% of the population, and type 2 diabetes, also known as non-insulin dependent diabetes mellitus, accounts for more than 80% of all cases. Type 2 diabetes is particularly prevalent in obese people aged over 40. Complications of type 2 diabetes include retinopathy and nephropathy, and diabetics have a significantly increased chance of suffering cardiovascular disease.

A number of drugs are available for the treatment of type 2 diabetes, but new ones, particularly those acting by novel mechanisms, are still needed. One such class of candidate therapeutic agents comprises inhibitors of dipeptidyl peptidase IV (DP-IV, EC.3.4.14.5). These compounds act, at least in part, by blocking the inactivation of endogenous incretins such as GLP-1 and GIP, resulting in an increased sensitivity to insulin and reduced post-prandial hyperglycaemia. To date, however, these compounds have only been examined as a method for controlling the management of blood glucose levels on an acute basis. The implications of long-term treatment with these compounds have not been considered.

SUMMARY OF THE INVENTION

We have now found that chronic treatment with inhibitors of DP-IV in a standard animal model of type 2 diabetes results in a delay in the development of the disease. Accordingly, one aspect of the present invention is a method of treating individuals at risk of developing type 2 diabetes, or in the early stages thereof, so as to prevent the progression of the disease, which method is to administer to the said individual repeated doses of a pharmaceutical composition comprising an inhibitor of DP-IV. Another aspect of the invention is a pharmaceutical composition for use in such treatment. A third aspect of the present invention is the use of inhibitors of DP-IV to prepare such compositions.

DETAILED DESCRIPTION OF THE INVENTION

We have examined the effects of chronic treatment of Zucker Diabetic Fatty (ZDF) rats with inhibitors of DP-IV. The ZDF rat is a well known model for human type 2 diabetes. ZDF rats are hyperphagic, and when fed on a high fat diet they become diabetic, as shown by hyperglycaemia, hypertriglyceridaemia, polydipsia and an increase in circulating free fatty acids. Disease onset is observed at about 8 weeks and the animals are fully diabetic by 11 weeks of age. We found that chronic treatment of ZDF rats with inhibitors of DP-IV leads to a significant delay in the onset of the diabetic state, which indicates that such chronic treatment will be useful in human subjects at risk of developing type 2 diabetes, or in the early stages of the disease.

Accordingly, a first aspect of the present invention is a method of treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease. The treatment comprises the administration to the said individual of repeated doses of an inhibitor of DP-IV.

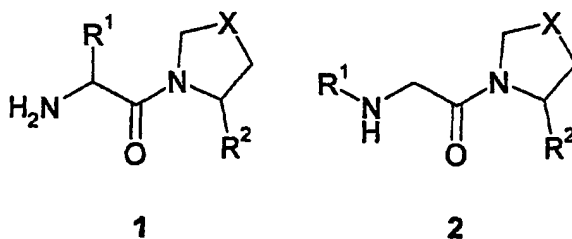
The assessment that an individual is at risk of developing type 2 diabetes will generally be made by an experienced physician, who will take into consideration such factors as the age and weight (and more specifically the body mass index, BMI) of the individual, as well as any history of diabetes in the individual's family and other risk factors. Similarly, a diagnosis of early-stage type 2 diabetes will be made by an experienced physician on the basis of a number of standard analyses and tests.

The inhibitor of DP-IV may be any compound that inhibits the enzymatic activity of DP-IV at a pharmacologically relevant dose. Suitable compounds can be identified as those that significantly inhibit the enzymatic activity of DP-IV in an *in vitro* assay at concentrations below 10 μ M. Particularly suitable compounds are those that inhibit the enzymatic activity of DP-IV at concentrations below 0.1 μ M. Such activity can be easily determined by one skilled in the art using one of the published assays. Suitable compounds should in addition preferably be selective, i.e. they should not significantly inhibit other unrelated enzymes at a concentration equal to that at which they inhibit DP-IV, and more preferably they should not inhibit such enzymes at a concentration ten-fold greater, even more preferably one hundred-fold greater, than that at which they significantly inhibit DP-IV.

The scope of the present invention extends to the use of prodrugs of DP-IV inhibitors. Prodrugs are well known in the art. A prodrug is a compound that is generally inactive *per se*, but which is subject to chemical or metabolic modification after administration, which modification causes the release of the active pharmaceutical agent. Prodrugs are typically used to increase oral bioavailability or to prolong the duration of action of a compound.

Examples of suitable compounds and methods for their preparation are disclosed in, for example, International Patent Applications WO91/16339, WO93/08259, WO95/15309, WO98/19998, WO99/46272, WO99/61431, WO99/67278, WO99/67279 and WO01/14318; US patents 5,462,928, 5,543,396, 5,939,560, 6,011,155, 6,107,317, 6,110,949, 6,124,305, 6,166,063 and 6,201,132; and European patent applications 0 528 858, 0 610 317, 0 731 789, 1 043 328, 1 050 540 and 1 082 314.

In a preferred embodiment of the present invention, the inhibitor of DP-IV is an α -aminoacyl pyrrolidide, an α -aminoacyl thiazolidide, an α -aminoacyl pyrrolidinenitrile, or an α -aminoacyl thiazolidinenitrile. In a more preferred embodiment, the inhibitor of DP-IV is a compound according to general formula 1 or general formula 2, or a pharmaceutically acceptable salt of either of these.

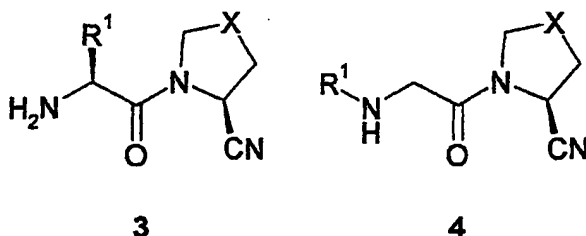


In these general formulae, X is selected from a methylene group CH_2 and a sulphur atom S; R^1 is selected from $\text{C}_1 - \text{C}_6$ alkyl groups, including branched and cyclic alkyl groups, and $(\text{CH}_2)_n\text{R}^3$; R^2 is selected from a hydrogen atom H and a nitrile group CN; R^3 is selected from NH-Het and NHCO-Het ; Het is a pyridyl, pyrimidyl or pyrazinyl group that is optionally substituted with up to two groups independently selected from methyl, Cl, F, CN and CF_3 ; and n is 2, 3, 4 or 5.

The compounds according to general formulae 1 and 2 all have at least one basic nitrogen atom and so are able to form addition salts with protic acids. Examples of such acids include hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid,

fumaric acid, maleic acid, citric acid, benzoic acid, pamoic acid and methanesulphonic acid. Insofar as these acids are pharmaceutically acceptable, such salts are included within the scope of the present invention.

The compounds according to general formula 1 have a stereogenic centre (asymmetric carbon atom) in the aminoacyl group. When R^2 is a nitrile, the compounds according to both general formulae have a stereogenic centre in the five-membered ring. Accordingly, these compounds can exist as optical isomers such as enantiomers and diastereomers. All such isomers are included within the scope of the present invention. The preferred stereochemistry is that illustrated in general formulae 3 and 4.



In a preferred embodiment of the present invention, the inhibitor is a compound according to general formula 1. More preferably, it is a compound according to general formula 1 wherein R^1 is a C_4 branched alkyl group such as sec-butyl or tert-butyl. Most preferably it is such a compound wherein X is CH_2 and R^2 is a nitrile, or X is S and R^2 is H.

In another preferred embodiment of the present invention, the inhibitor is a compound according to general formula 2. More preferably, it is a compound according to general formula 2 wherein R^1 is $(CH_2)_nR^3$, n is 2 and R^3 is NH-Het. Most preferably it is such a compound wherein X is CH_2 , R^2 is a nitrile, and Het is 5-cyano-2-pyridyl.

In the method of treatment according to the present invention, the inhibitor of DP-IV will be administered to the individual as a pharmaceutical composition such as, for example, a tablet, capsule, powder, suppository, solution or suspension. The general principles for the preparation of such formulations are well known in the art. The formulation may further comprise such pharmaceutically acceptable excipients as bulking agents, binding agents, preservatives, solvents, flavoring agents and the like. It may further include one or more additional pharmacologically active agents, such as anti-diabetic agents, but preferably the DP-IV inhibitor is the sole active agent.

The formulation may be administered by any appropriate route, including oral, buccal, sublingual, rectal, intravaginal and transdermal administration as well as by intravenous, subcutaneous and intramuscular injection. Preferably the formulation is administered orally as a tablet or capsule.

The dose will be determined by the attending physician, taking into consideration all the relevant factors. Typically a single dose will comprise between 1mg and 1000mg, preferably between 5mg and 250mg. The dose may be given once per day or more often, such as twice or three times per day. Treatment will be continued for an extended period of time such as several weeks, months or even years.

Alternatively, the formulation may be administered as a depot which releases active compound over a period of between one week and three months. Such controlled-release formulations are known in the art, and generally comprise a pharmaceutically active species associated with a biocompatible polymer. The polymer may simply encapsulate the active agent, forming a physical barrier to its release into the general circulation, or there may be a chemical association, such as a covalent or ionic interaction, between the polymer and the active agent. Such formulations are generally administered by intramuscular or subcutaneous injection. In this case, the administration will be repeated at intervals of one week up to three months so as to maintain treatment over an extended period.

A second aspect of the present invention is a pharmaceutical composition for the treatment of a person at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay or prevent the progression of the disease. The composition comprises an inhibitor of DP-IV as described above, suitably formulated, together with instructions for repeated dosing.

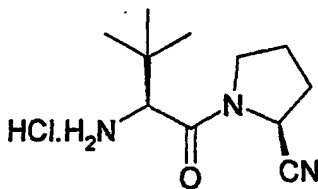
A third aspect of the present invention is the use of an inhibitor of DP-IV for the preparation of a pharmaceutical composition for the treatment of a person at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay or prevent the progression of the disease.

EXAMPLES

Example 1 – Preparation of inhibitors of DP-IV

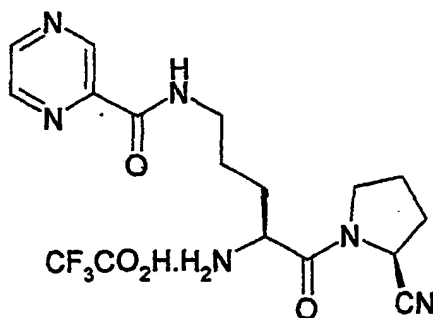
Inhibitors of DP-IV can be prepared according to published methods.

Example 1A – (2S)-1-((2'S)-2'-amino-3',3'-dimethylbutanoyl)pyrrolidine-2-carbonitrile hydrochloride

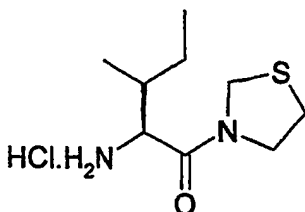


The title compound is prepared according to the methods of WO95/15309, and particularly of Example 13 therein. Briefly, BOC-protected *tert*-butylglycine is coupled to prolineamide, the primary amide function is dehydrated with trifluoroacetic anhydride to give the nitrile, and the BOC-group is removed with HCl in dioxan.

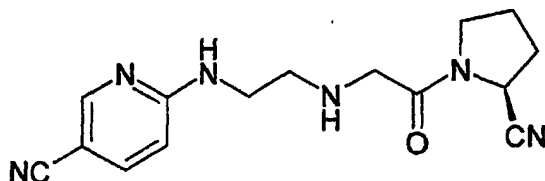
Example 1B – (2S)-1-((2'S)-2'-amino-5'-pyrazinecarbonylamino-pentanoyl)pyrrolidine-2-carbonitrile trifluoroacetate



The title compound is prepared according to the method of Example 1A above. Briefly, *N*^α-BOC-protected *N*^ε-pyrazinecarbonylornithine is coupled to prolineamide, the primary amide function is dehydrated with trifluoroacetic anhydride to give the nitrile, and the BOC-group is removed with trifluoroacetic acid.

Example 1C – N-Isoleucylthiazolidine hydrochloride

The title compound is prepared according to the standard methods. Briefly, BOC-protected isoleucine is coupled to thiazolidine and the BOC-group is removed with HCl in dioxan.

Example 1D – (2S)-1-((2'-(5''-Cyano-2''-pyridylamino)ethylamino)acetyl)pyrrolidine-2-carbonitrile

The title compound is prepared according to the methods of WO98/19998, and particularly of Example 3 therein. Briefly, bromoacetyl bromide is reacted with prolineamide and the product is dehydrated with trifluoroacetic anhydride to give N-bromoacetylpyrrolidine-2-carbonitrile. This is treated with 2-(5-cyano-2-pyridylamino)ethylamine to give the product.

Example 2 – Inhibition of DP-IV *in vitro*

The *in vitro* inhibitory action of the compounds is determined in a fluorimetric assay. Human DP-IV is incubated with a standard substrate, Ala-Pro-AFC, in the presence of various concentrations of the inhibitor. The reaction is monitored by measuring the increase in fluorescence due to the reaction product, AFC. Using standard manipulations, an inhibitory constant, K_i , is determined. Typical results are given below.

Compound of Example No.	K_i (nM)
1A	1.0
1B	0.4
1C	33.0
1D	5.0

Example 3 – Effect of long-term inhibition of DP-IV in ZDF rat

Male ZDF rats, aged 6.5 weeks at the beginning of the study (day 0), are given the compound of Example 1A (10mg/kg p.o.) once or twice per day for four weeks. Control animals are given vehicle. A group of untreated lean rats is used as a comparison. Glycaemia, insulinaemia, body weight, food and water intake, and plasma triglyceride and free fatty acid levels are monitored throughout the study.

Example 3A - Glycaemia

At the start of the study glycaemia is not significantly different in the obese animals compared to the lean rats. At day 8, the obese control group develop hyperglycaemia, which increases and reaches a plateau by day 19. The animals treated once daily with the inhibitor do not develop significant hyperglycaemia until day 15, and those treated twice daily do not develop significant hyperglycaemia until day 24. The results are presented in Figure 1.

Example 3B – Insulinaemia

All three groups of obese animals show elevated plasma insulin concentrations at the beginning of the study period. In the control obese animal group, the insulin concentration rises rapidly to reach a peak by day 8 before decreasing as the islet β -cells die. In the group treated once daily with the inhibitor a similar pattern is observed, but the peak insulin level is only reached on day 11. In the group treated twice daily with the inhibitor insulin concentration does not attain the same high level, and there is evidence of β -cell survival at the end of the study period. The results are presented in Figure 2.

Example 3C – Body weight gain

All three groups of obese animals gain weight faster than the lean group, but the group treated twice daily with the inhibitor gain less weight than the control obese group and the group treated once daily. The results are presented in Figure 3.

Example 3D – Food and water Intake

All three groups of obese animals eat more than the lean group, but from day 17 the food intake for the group treated twice daily is significantly less than that for the control obese group and the once-daily treatment group. From day 10, the control and once-daily

treatment groups show an increase in their water consumption, but the twice-daily treatment group maintains a normal water intake. The results are presented in Figures 4 and 5.

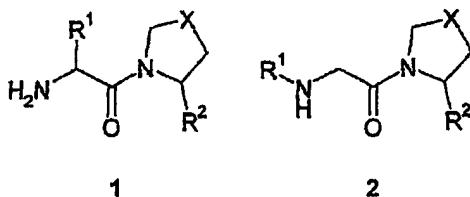
Example 3E – Plasma free fatty acid and triglyceride levels

Plasma free fatty acid and triglyceride levels are significantly elevated in the obese animals at day 0, and in control obese animals they increase throughout the study period. Once-daily, and particularly twice-daily treatment attenuates this increase. The results are presented in Figures 6 and 7.

The results described above clearly indicate that long-term inhibition of DP-IV is effective in delaying the onset of diabetic symptoms in the ZDF rat, and hence that inhibitors of DP-IV should be useful as prophylactic agents for people at risk of developing type 2 diabetes and as a treatment for people in the early stages of the disease to delay the progression of diabetic complications.

CLAIMS

- 1 A method of treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease, which comprises the administration to the individual of repeated doses of an inhibitor of dipeptidyl peptidase IV or a prodrug thereof.
- 2 A method according to Claim 1 in which each dose of inhibitor of dipeptidyl peptidase IV or prodrug thereof is released over a period of between one week and three months.
- 3 A method according to Claim 1 or 2 in which each dose is a depot formulation.
- 4 A method according to Claim 1, 2 or 3 in which the repeated doses maintain the treatment over an extended period.
- 5 A method according to any preceding claim in which the inhibitor of dipeptidyl peptidase IV is an α -aminoacyl pyrrolidide, an α -aminoacyl thiazolidide, an α -aminoacyl pyrrolidinenitrile or an α -aminoacyl thiazolidinenitrile.
- 6 A method according to any preceding claim in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or general formula 2, or a pharmaceutically acceptable salt thereof



wherein: X is selected from CH₂ and S;

R¹ is selected from C₁ – C₆ alkyl and (CH₂)_n; R³;

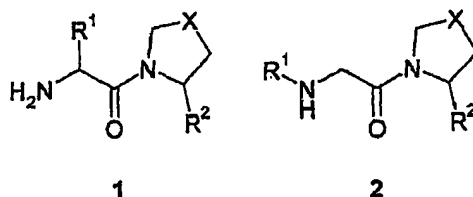
R² is selected from H and CN;

R³ is selected from NH-Het and NHCO-Het; and

Het is a pyridyl, pyrimidyl or pyrazinyl group that is optionally substituted with

up to two groups independently selected from methyl, Cl, F, CN and CF₃; and n is 2, 3, 4 or 5.

- 7 A method according to any preceding claim in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or a pharmaceutically acceptable salt thereof wherein R¹ is C₄ alkyl.
- 8 A method according to any of claims 1 to 6 in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 2, or a pharmaceutically acceptable salt thereof, wherein X is CH₂, R² is CN, R³ is NH-Het, Het is a 5-cyano-2-pyridyl group, and n is 2.
- 9 A pharmaceutical composition for treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease, comprising an inhibitor of dipeptidyl peptidase IV or a prodrug thereof.
- 10 A composition according to claim 9 which releases the inhibitor of dipeptidyl peptidase IV or prodrug thereof over a period of between one week and three months.
- 11 A composition according to Claim 9 or 10 which is a depot formulation.
- 12 A composition according to any of claims 9, 10 or 11 for treating the individual over an extended period.
- 13 A composition according to any of claims 9 to 12 wherein the inhibitor of dipeptidyl peptidase IV is an α -aminoacyl pyrrolidide, an α -aminoacyl thiazolidide, an α -aminoacyl pyrrolidinenitrile or an α -aminoacyl thiazolidinenitrile.
- 14 A composition according to any of claims 9 to 13 wherein the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or general formula 2, or a pharmaceutically acceptable salt thereof



wherein: X is selected from CH₂ and S;

R¹ is selected from C₁ – C₆ alkyl and (CH₂)_n R³;

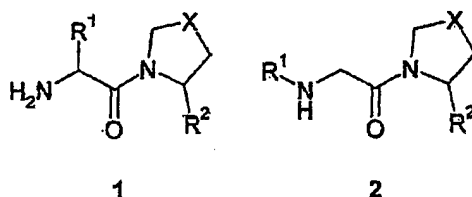
R² is selected from H and CN:

R³ is selected from NH-Het and NHCO-Het; and

Het is a pyridyl, pyrimidyl or pyrazinyl group that is optionally substituted with up to two groups independently selected from methyl, Cl, F, CN and CF₃; and n is 2, 3, 4 or 5.

- 15 A composition according to any of claims 9 to 14 wherein the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or a pharmaceutically acceptable salt thereof wherein R^1 is C_4 alkyl.
- 16 A composition according to any of claims 9 to 14 wherein the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 2, or a pharmaceutically acceptable salt thereof, wherein X is CH_2 , R^2 is CN, R^3 is NH-Het, Het is a 5-cyano-2-pyridyl group, and n is 2.
- 17 The use of an inhibitor of dipeptidyl peptidase IV or a prodrug thereof for the preparation of a medicament for treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease.
- 18 The use according to claim 17 wherein the medicament releases the inhibitor of dipeptidyl peptidase IV or prodrug thereof over a period of between one week and three months.
- 19 The use according to claim 18 wherein the medicament is a depot formulation.

- 20 The use according to any of claims 17, 18 or 19 wherein the medicament is for treatment of the individual over an extended period.
- 21 The use according to any of claims 17 to 20 in which the inhibitor of dipeptidyl peptidase IV is an α -aminoacyl pyrrolidide, an α -aminoacyl thiazolidide, an α -aminoacyl pyrrolidinenitrile or an α -aminoacyl thiazolidinenitrile.
- 22 The use according to any of claims 17 to 21 in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or general formula 2, or a pharmaceutically acceptable salt thereof



wherein: X is selected from CH₂ and S;

R¹ is selected from C₁ – C₆ alkyl and (CH₂)_n; R³;

R² is selected from H and CN;

R³ is selected from NH-Het and NHCO-Het; and

Het is a pyridyl, pyrimidyl or pyrazinyl group that is optionally substituted with up to two groups independently selected from methyl, Cl, F, CN and CF₃; and n is 2, 3, 4 or 5.

- 23 The use according to any of claims 17 to 22 in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 1 or a pharmaceutically acceptable salt thereof wherein R¹ is C₄ alkyl.
- 24 The use according to any of claims 17 to 22 in which the inhibitor of dipeptidyl peptidase IV is a compound according to general formula 2, or a pharmaceutically acceptable salt thereof, wherein X is CH₂, R² is CN, R³ is NH-Het, Het is a 5-cyano-2-pyridyl group, and n is 2.

- 25 The use of an inhibitor of dipeptidyl peptidase IV or a prodrug thereof for the preparation of a pharmaceutical composition for repeatedly treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease.
- 26 The use according to claim 25 for the preparation of a pharmaceutical composition which releases the inhibitor of dipeptidyl peptidase IV or prodrug thereof over a period of between one week and three months.
- 27 The use according to claim 25 or 26 in which the pharmaceutical composition is a depot formulation.
- 28 A method of treating an individual at risk of developing type 2 diabetes, or in the early stages thereof, so as to delay the onset and progression of the disease, which comprises the administration to the individual of a depot formulation of an inhibitor of dipeptidyl peptidase IV or a prodrug thereof.
- 29 A method according to Claim 28 in which the depot formulation releases the inhibitor of dipeptidyl peptidase IV or prodrug thereof over a period of between one week and three months.
- 30 A method according to Claim 28 or 29 in which repeated doses of the depot formulation are administered to maintain the treatment over an extended period.

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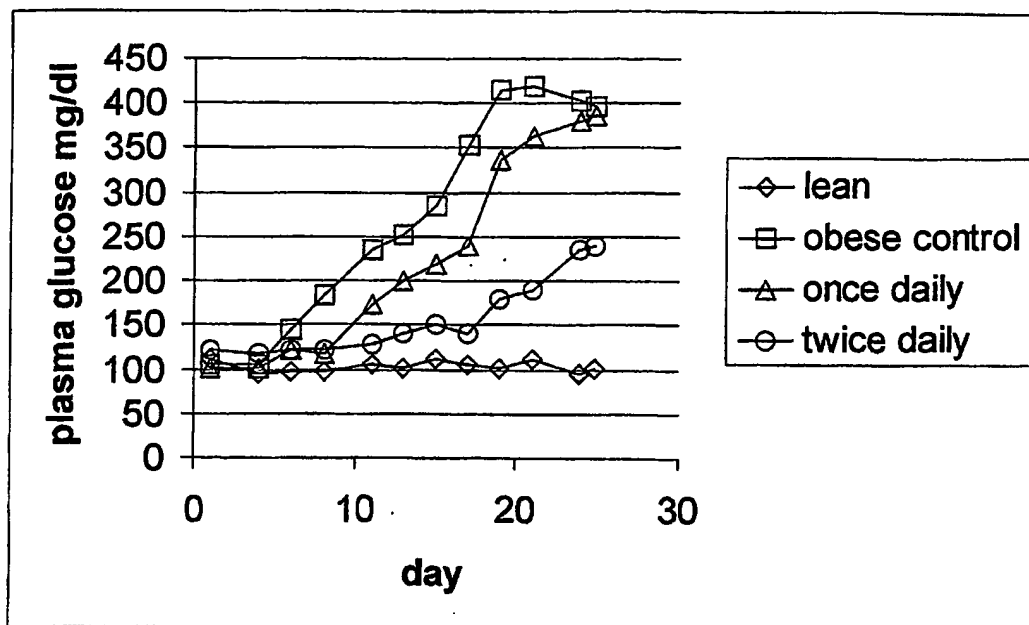


Figure 1 - Blood glucose concentration

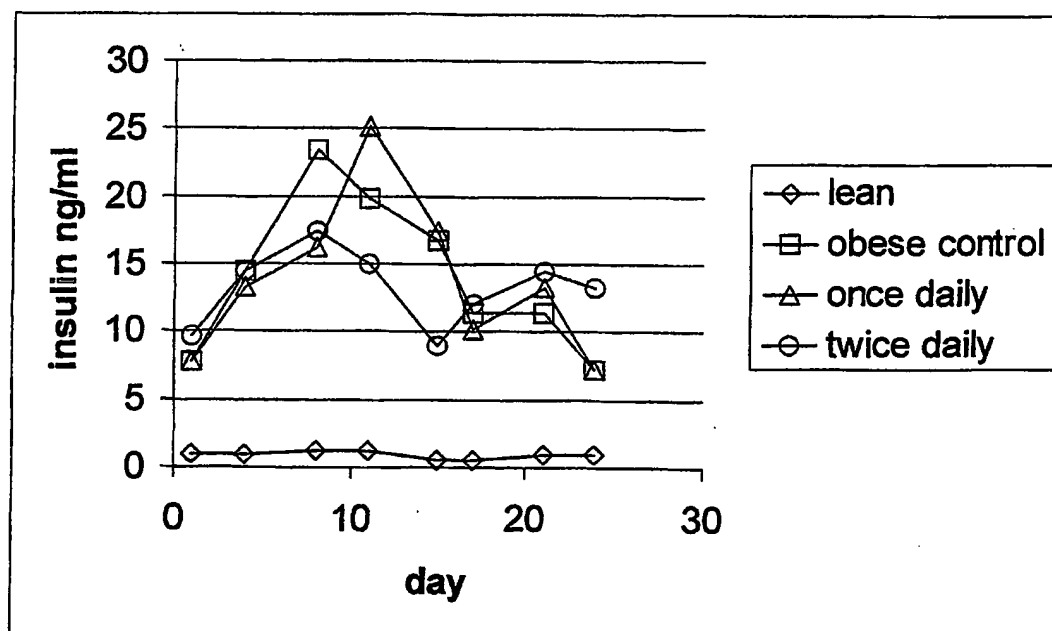


Figure 2 - Plasma insulin concentration

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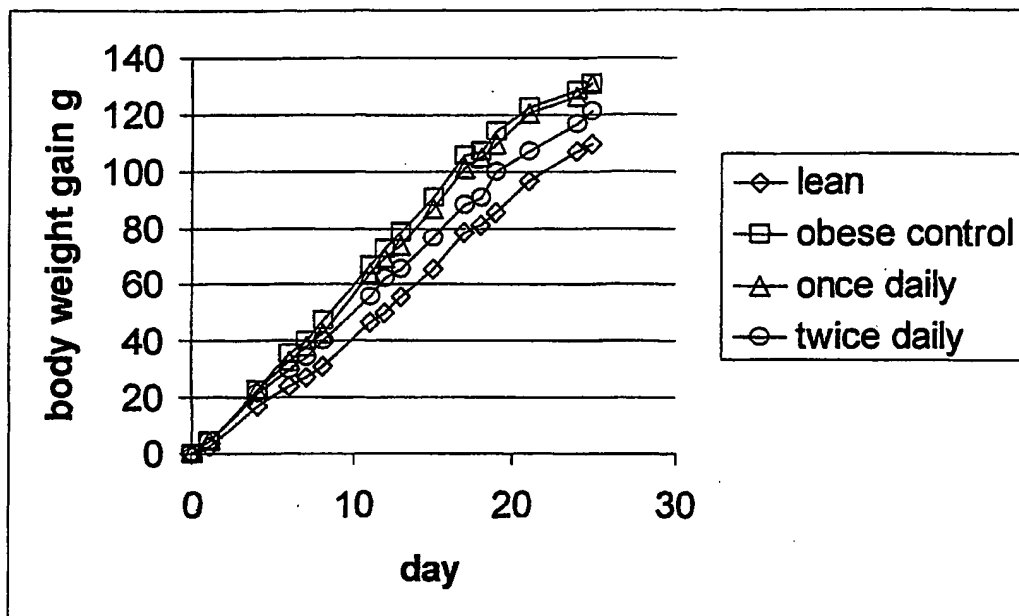


Figure 3 – Body weight gain

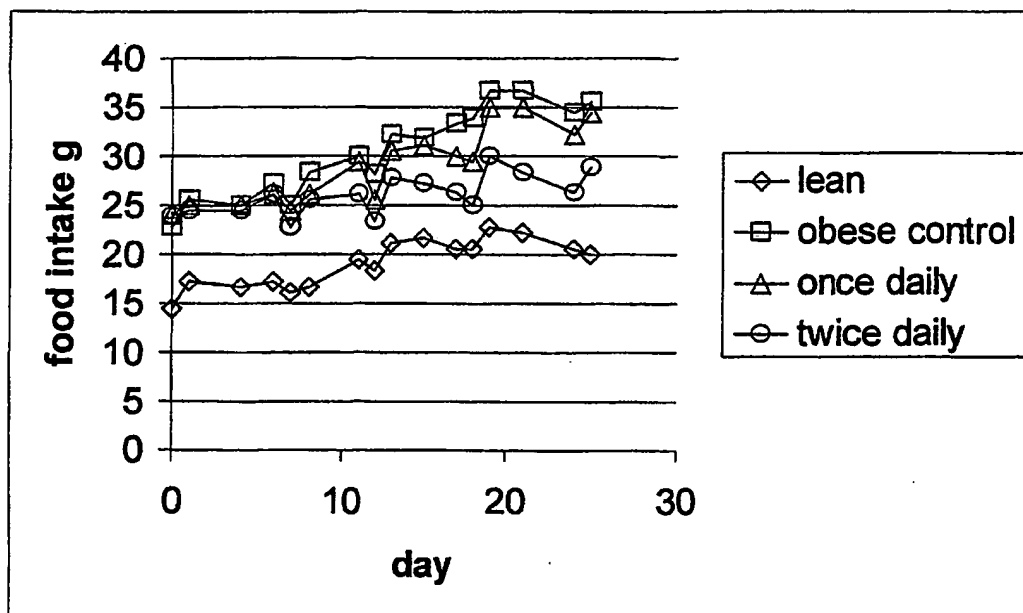


Figure 4 – Food consumption

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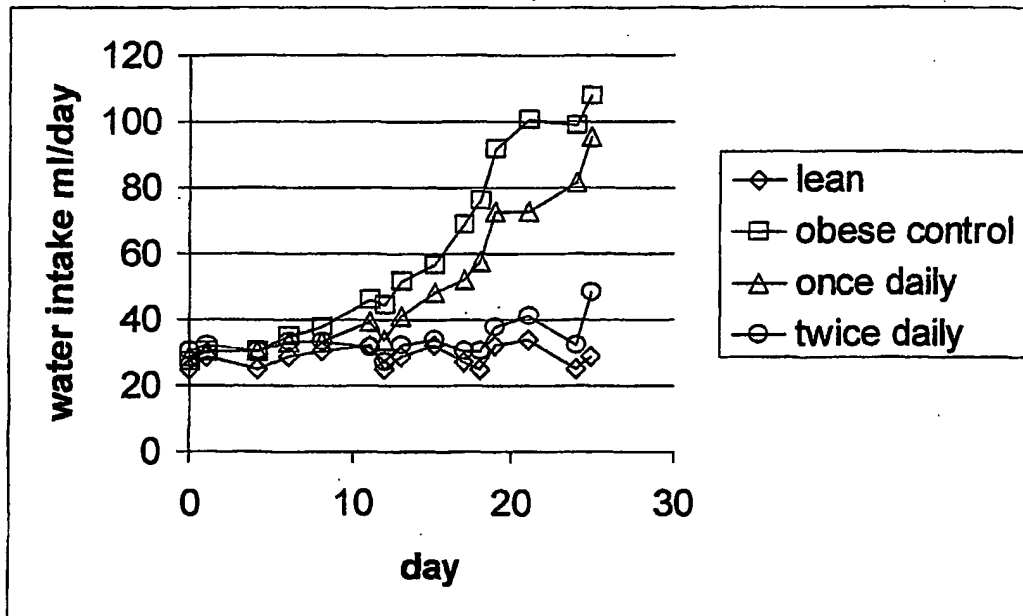


Figure 5 – Water intake

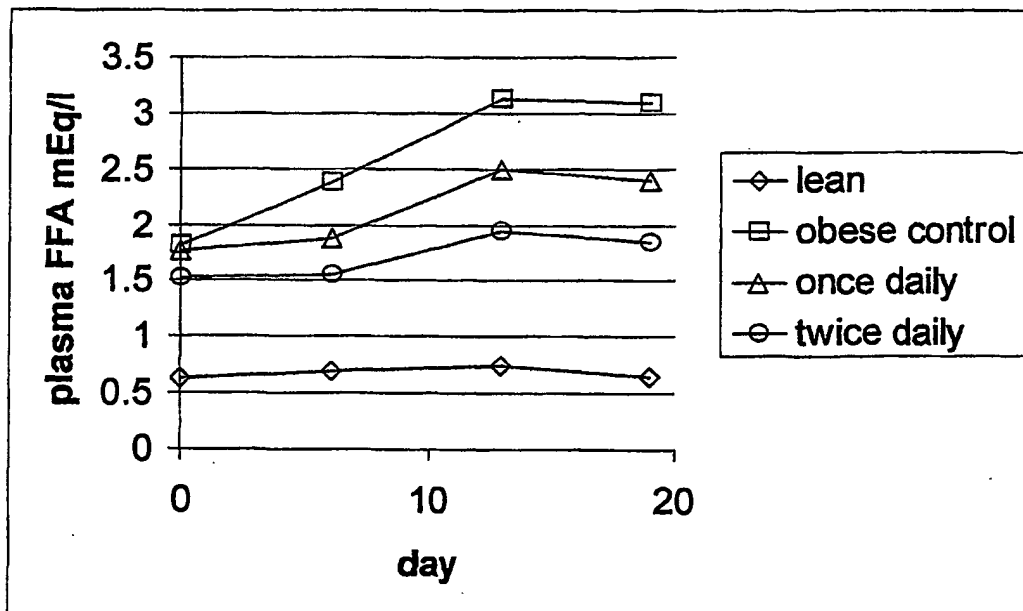


Figure 6 – Blood free fatty acid concentration

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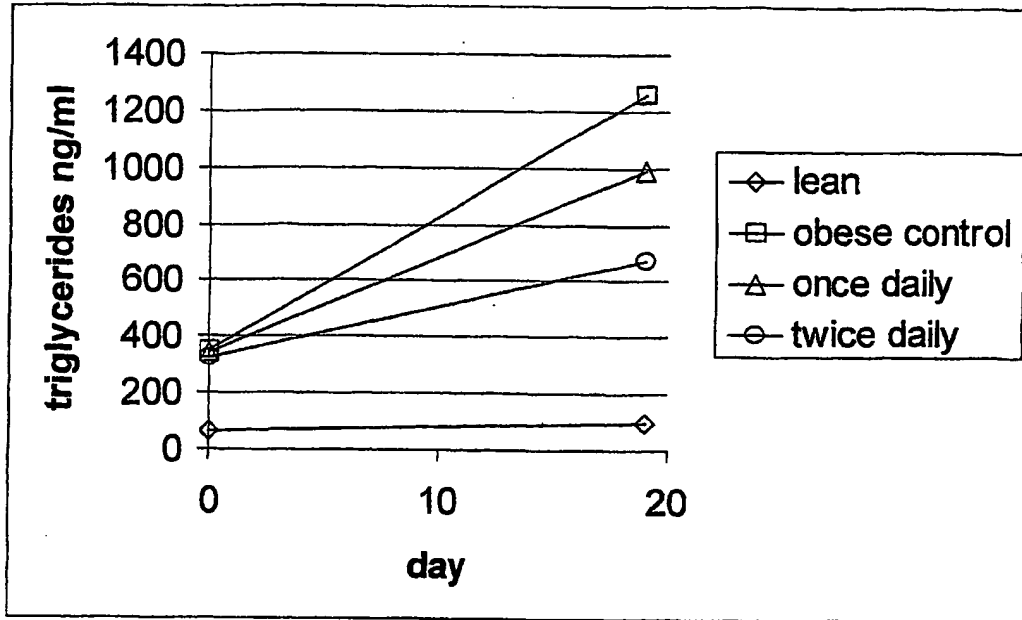


Figure 7 – Blood triglyceride concentration

INTERNATIONAL SEARCH REPORT

In International Application No

F 01, GB 02/01674

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/40 A61K31/497 A61K31/426 A61K31/4439
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HOLST J J ET AL: "INHIBITION OF THE ACTIVITY OF DIPEPTIDYL-PEPTIDASE IV AS A TREATMENT FOR TYPE 2 DIABETES" DIABETES, NEW YORK, NY, US, vol. 47, November 1998 (1998-11), pages 1663-1670, XP000853619 ISSN: 0012-1797 abstract page 1666, column 1, paragraph 3 - paragraph 4 page 1667, column 2, paragraph 2 - paragraph 3 page 1668, column 2, paragraph 3 -page 1669, column 1, paragraph 2</p> <p style="text-align: center;">-/--</p>	<p>1,2,4,9, 10,12, 17,18, 20,25,26</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

31 July 2002

Date of mailing of the international search report

06/08/2002

Name and mailing address of the ISA

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Authorized officer

Cielen, E

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/GB 02/01674

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 47219 A (LU HUANG HUI ; ONTOGENY INC (US); PANG KEVIN (US)) 17 August 2000 (2000-08-17)	1-4, 9-12, 17-20, 25-30
Y	page 6, line 5 - line 9 page 6, line 29 - line 30 page 7, line 9 - line 11 page 19, line 7 - line 9 page 19, line 30 - page 20, line 2 page 24, line 28 - line 29 page 34, line 10 - line 12 page 35, line 23 - line 28 page 39, line 21 - line 24 page 40, line 27 - line 31 page 41, line 22 - line 27 page 42, line 20 - line 32 page 44, line 7 - line 13 claims 1,2,21,23,24,28-32	1-24
X	WO 97 40832 A (PAULY ROBERT P ; PEDERSON RAY A (CA); MCINTOSH CHRISTOPHER H S (CA)) 6 November 1997 (1997-11-06)	1,5-7,9, 13-15, 17, 21-23,25
Y	abstract page 5, line 5 - line 28 page 6, line 11 - line 14 claims 2,3	1-7, 9-15, 17-23
X	US 6 124 305 A (VILLHAUER EDWIN BERNARD) 26 September 2000 (2000-09-26) cited in the application	9,13,14, 16
Y	abstract column 1, line 35 - column 2, line 35 column 6, line 42 - line 46 column 10, line 48 - line 49 examples 1-4,6,7,9,32,38,43,50,52,55,56,59,60,62-64 claims	1-6, 8-14, 16-22,24
X	US 6 107 317 A (VILLHAUER EDWIN BERNARD) 22 August 2000 (2000-08-22) cited in the application	9,13,14
Y	abstract column 3, line 5 - line 61 column 5, line 14 - line 47 column 8, line 26 - line 33 column 9, line 5 - line 7 examples 1,3,4 claims	1-6, 9-14, 17-22
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 110 949 A (VILLHAUER EDWIN BERNARD) 29 August 2000 (2000-08-29) cited in the application	9,13,14
Y	abstract column 3, line 11 - line 61 column 5, line 3 - line 36 column 11, line 19 - line 31 column 12, line 3 - line 4 example 1 claims	1-6, 9-14, 17-22
X	WO 99 61431 A (GLUND KONRAD ;KRUBER SUSANNE (DE); DEMUTH HANS ULRICH (DE); PROBIO) 2 December 1999 (1999-12-02) abstract page 1, paragraph 1 - paragraph 2 page 3, paragraph 3 page 4, paragraph 2 - paragraph 3 page 5, paragraph 4 page 6, paragraph 1 -page 8, paragraph 1 page 10, paragraph 1 page 10, paragraph 3 -page 11, paragraph 1 page 11, paragraph 3 page 17, paragraph 2 -page 18, paragraph 7 claims 5,6,11,15,18	1,2,4-7, 9,10, 12-15, 17,18, 20-23, 25,26
X	DE 299 09 208 U (PROBIODRUG GES FUER ARZNEIMITT) 9 September 1999 (1999-09-09) page 1, paragraph 1 - paragraph 2 page 4, paragraph 2 - paragraph 3 page 5, paragraph 5 -page 6, paragraph 5 page 7, paragraph 3 page 8, paragraph 5 page 9, paragraph 3 page 10, paragraph 2 page 16, paragraph 2 -page 17, paragraph 4 claims 5,9,11,12	1,2,4-6, 9,10, 12-14, 17,18, 20-22, 25,26
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 166 063 A (VILLHAUER EDWIN BERNARD) 26 December 2000 (2000-12-26) cited in the application abstract column 1, line 19 - line 30 column 4, line 8 - line 29 column 5, line 50 - column 6, line 6 column 6, line 47 - line 48 claims 5,8 ---	1,5,9, 13,17, 21,25
X	WO 00 56296 A (BROQUA PIERRE ;FERRING BV (NL)) 28 September 2000 (2000-09-28) page 1, paragraph 3 -page 2, paragraph 3 page 5, paragraph 1 - paragraph 4 example 1B claims 1,3 ---	9,10, 12-16
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P,X	WO 01 40180 A (EVANS DAVID MICHAEL ;FERRING BV (NL)) 7 June 2001 (2001-06-07) page 3, paragraph 1 page 17, paragraph 2 -page 18, paragraph 2 ---	1,3-5,9, 11-13, 17, 19-21, 25,27, 28,30
P,X	WO 01 81337 A (EVANS DAVID MICHAEL ;PITT GARY ROBERT WILLIAM (GB); FERRING BV (NL) 1 November 2001 (2001-11-01) abstract page 2, paragraph 2 - paragraph 3 page 5, paragraph 1 - paragraph 2 page 7, paragraph 2 page 8, paragraph 1 - paragraph 2 examples 1,4-11,15-25,30,31,37-47,50-53,59-67,70-72 ,74 examples 79-83,92-101,103,106-111,116,118-120 ---	1,4-6,9, 12-14, 17, 20-22,25

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Int'l Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>WO 01 34594 A (JACKSON PAUL ;STEINER JOSEPH (US); GUILFORD PHARM INC (US)) 17 May 2001 (2001-05-17) page 5, line 8 - line 10 page 9, line 15 - line 20 page 10, line 3 - line 5 page 12, line 8 - line 10 page 13, line 1 - line 6 page 16, line 4 -page 17, line 17 examples 19-22,24-27,31-33,55,65,70,77,79,82,83,86, 87,89,91 page 47, line 6 -page 48, line 26 claim 4</p>	9,11-14, 16
X	<p>FREYSE E J ET AL: "Long-term metabolic effect of daily oral application of DPIV-inhibitor P32/98 in diabetic Zucker rats (fa/fa)." DIABETOLOGIA, vol. 43, no. Supplement 1, August 2000 (2000-08), page A67 XP008005148 36th Annual Meeting of the European Association for the Study of Diabetes;Jerusalem, Israel; September 17-21, 2000 ISSN: 0012-186X</p>	9,10, 12-15
A	<p>the whole document</p>	1,2,4-7, 17,18, 21-23, 25,26
X	<p>BRAND CHRISTIAN L ET AL: "Chronic administration of valine pyrrolidide, a selective inhibitor of dipeptidyl peptidase IV, improves glucose tolerance without affecting food intake in Zucker Obese rats." DIABETES, vol. 48, no. SUPPL. 1, 1999, page A271 XP008005144 59th Scientific Sessions of the American Diabetes Association;San Diego, California, USA; June 19-22, 1999 ISSN: 0012-1797</p>	9,10,13, 14
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International Application No

PCT/GB 02/01674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BALKAN B ET AL: "Sustained improvement of glucose tolerance by DPP-IV inhibition after chronic treatment with NVP-DPP728." DIABETOLOGIA, vol. 42, no. SUPPL. 1, August 1999 (1999-08), page A41 XP008005150 35th Annual Meeting of the European Association for the Study of Diabetes; Brussels, Belgium; September 28-October 2, 1999 ISSN: 0012-186X	9,10, 12-14,16
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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-8 and 28-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5, 9-13, 17-21, 25-30 relate to a compound which actually is not well-defined. The use of the definitions "an inhibitor of dipeptidyl peptidase IV", "a prodrug thereof", "an alpha-aminoacyl pyrrolidide", "an alpha-aminoacyl thiazolidide", "an alpha-aminoacyl pyrrolidinenitrile", "an alpha-aminoacyl thiazolidinenitrile" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. Moreover, the use of the definition "over an extended period" in claims 4, 12, 20 in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds as disclosed in the Markush formulae of claims 6-8, 14-16 and 22-24.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

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